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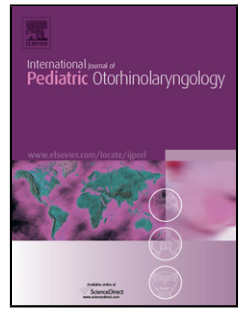

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Title page

Outcomes after adenotonsillectomy using a fixed anesthesia protocol in children with obstructive sleep apnea

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Authors' contributions: K.D.P. designed the study, wrote the manuscript and performed critical revisions. A.I performed data collection, performed and interpreted statistical tests and wrote the manuscript.

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Objective

To document the effects of a fixed anesthesia protocol on peri-operative events in children undergoing adenotonsillectomy for obstructive sleep apnea (OSA).

Methods

A non-randomized prospective study was conducted during the years 2011 to 2013 within a setting of a tertiary-level university hospital. Sixty five children with polysomnographically-proven OSA undergoing adenotonsillectomy were enrolled in the study and stratified into three groups based on severity. The relationship between severity of OSA as determined by apnea-hypopnea index (AHI) and oxygen saturation (SpO_2) nadir were compared with time taken to (i) extubation following emergence and (ii) discharge from the post-anesthesia care unit. Adjustments were made in the dosages of premedication (midazolam) and opioid analgesic administered following induction (hydromorphone) depending on the severity of OSA. A non-validated but fixed anesthesia protocol tailored to the severity of OSA was used in all patients. In addition, all adverse events were also monitored.

Results

A paradoxical, yet significant reduction in emergence time was observed among patients with severe OSA following surgery (ANOVA, Tukey-Kramer post-hoc tests, $P < 0.001$). There were also fewer adverse events in this group.

Conclusions

Emergence from anesthesia after adenotonsillectomy may be positively influenced by an anesthetic technique titrated according to the severity of OSA. Adverse respiratory events due to the severity of sleep apnea and attendant hypoxemia may be minimized and outcomes improved with similarly tailored protocols.

1. Introduction

Obstructive sleep apnea (OSA) in childhood is a commonly diagnosed condition, affecting about 1-4% of all children [1–3]. Polysomnography (PSG) remains the gold standard for the objective diagnosis as well as estimation of severity of OSA [4,5]. Pediatric OSA is generally treated by adenotonsillectomy and the effectiveness of the procedure has been validated by numerous meta-analyses [6,7]. However, with increase in the incidence of childhood obesity, the response of OSA to adenotonsillectomy has been somewhat blunted [7,8]. Notwithstanding this, obese and overweight children undergoing the procedure still demonstrate significant improvement in polysomnography (PSG) indices as well as quality of life despite the reduced overall efficacy.

It is well accepted that individuals with OSA are prone to the cardio-pulmonary depressant effects of peri-operative opioids and benzodiazepines in addition to the tendency towards upper airway obstruction [9–12]. This heightened sensitivity seen peri-operatively warrants appropriate monitoring in the post anesthesia care unit (PACU) and on the in-patient unit, airway control throughout the peri-operative period, and judicious use of medications.

The predisposition towards arterial hypoxemia during sleep has ramifications for the optimal anesthetic management of children undergoing adenotonsillectomy for OSA [13]. Sanders et al. [14] studied the incidence of complications following adenotonsillectomy in children with OSA and found that supraglottic obstruction, breath holding, and desaturation on anesthetic induction and emergence were the most common adverse events. The authors also identified increased severity of OSA, low body weight, and young age as factors that increased the risk of peri-operative of adverse events. However, other investigators have postulated that this increase in risk could be attributed to nonspecific up regulation of μ-opioid receptors in the brainstem by exposure to recurrent hypoxemia as seen in animal models thereby increasing sensitivity to therapeutic doses of the drug [15]. Physiological correlates have been observed in children with OSA as well as those experiencing hypoxemia as a consequence of high altitude [16]. These studies suggest that certain events during and following surgery for OSA in children could be influenced by pharmacologic manipulation of anesthesia and analgesia [13]. However, literature on the subject is

sparse and there is a lack of prospective controlled studies examining modifications to current anesthetic regimens. Encouraged by results seen in animal models as well as literature showing the physiologic benefits of lowered doses of opioids in patients with OSA, we hypothesized that an anesthetic regimen tailored to the severity of OSA by modifying sedative and analgesic dosages would have the potential to positively impact emergence and peri-operative events following adenotonsillectomy for OSA in children. We observed the effects of SpO_2 nadir and AHI on the duration of emergence and recovery from anesthesia as well as the frequency and severity of adverse peri-operative events.

2. Methods

2.1. Enrollment of subjects

All protocols and procedures were approved by the Institutional Ethical Review Board of the University Of Maryland School of Medicine. Patients with PSG-proven OSA scheduled for adenotonsillectomy were enrolled based on the criteria in Table 1. Sample size of 65 was calculated to give the study a power > 80 [17].**The study was conducted from July 2011 to January 2013.**

2.2. Polysomnographic criteria for severity of OSA

Diagnosis of OSA was established by polysomnography with an AHI ≥ 2. Further stratification into groups was based on:

a. Mild OSA: AHI <5; SpO_2 nadir > 85%
b. Moderate OSA: AHI = 5-20; SpO_2 nadir = 75-85%
c. Severe OSA: AHI > 20; SpO_2 nadir < 75%

2.3. Anesthetic regimen and determination of endpoints

The anesthetic technique used for this study was developed by the division of pediatric anesthesia at our hospital and is not validated. We also used their grading of OSA severity since the protocol for dosing was based on it. Figure 1 shows a flow diagram illustrating the steps and dosing in the anesthetic regimen used in this study. Adjustments were made in doses of premedication (midazolam, 0.5-1 mg/kg; doses

were given **through IV, PO or rectal routes after ensuring bioequivalence [Fig. 1]** depending on OSA group) and opioid analgesic administered following induction (hydromorphone, 5-10 µg/kg IV). Two endpoints were determined—the first that of "emergence time", as determined by the time between discontinuation of anesthesia and that taken to meet extubation criteria i.e. regular respiration, grimaces and/or purposeful movements and the second, the "recovery time", defined as the time between arrival to the PACU and when the patient met criteria for discharge. Discharge criteria were met by patients when the modified Aldrete score was recorded to be > 9. The Aldrete or post anesthesia recovery score assesses transition from discontinuation of anesthesia until return of protective reflexes and motor function [18].

2.4. Determination of adverse events

A *respiratory event* was defined as an airway event requiring medical intervention in order to prevent harm to the patient. These events as well as the respective interventions were recorded during emergence as well as the post-operative period. These were documented as (i) number of mild oxygen desaturations (85-93%) (ii) number of severe desaturations (< 85%) and (iii) number of laryngospasms. The interventions were recorded as (i) jaw thrust (ii) placement for oral or nasal airway and (iii) reintubation.

2.5. Data analysis

Data records were obtained and exported to MATLAB (The Mathworks, Natwick, MA) software for further analysis. Distributions of data were first examined for normality. Basic PSG indices were recorded as a function of extubation and recovery times. Differences were statistically analyzed using analysis of variance (ANOVA) as implemented by the Statistics Toolbox™ within Matlab. If significant differences were observed in the initial ANOVA, a pair-wise Tukey multiple comparisons test was employed to examine differences between OSA groups. In the next step, a regression analysis was carried out to examine the relationship between PSG indices and recovery times. Slopes were determined from these functions following an analysis of covariance (ANCOVA)—subsequent to which they were tested whether they were significantly different from zero.

3. Results

3.1. Descriptive statistics

65 individuals were enrolled in the study (M:F; n = 36:29). Mean ± s.d. age of the enrolled population was 4.6 ± 1.9 years and the weight was 19.9 ± 6.38 kg **(BMI z-score = 0.52 ± 0.59).** From PSG-derived indices, mean AHI was 17.8 ± 12.0 and mean SpO_2 nadir was 83.2 ± 10.4%. Mean ± s.d. of overall emergence time was 16.4 ± 6.8 min and the recovery time was 123.72 ± 46.0 min. Histograms showing group-wise distributions of key characteristics are shown in Figure 2. Each panel within the figure also shows the mean ± s.d above.

3.2. Differences between OSA groups

Demographically, the three groups were similar to each other. The ages ($F_{2,62} = 1.43$, $P = 0.25$, ANOVA) and weights ($F_{2,62} = 1.34$, $P = 0.27$) were not significantly different between OSA groups. Airway events were generally rare. Importantly, there was no difference in the incidence of airway events either in the OR ($F_{2,62} = 1.22$, $P = 0.3$) or in the PACU ($F_{2,62} = 2.15$, $P = 0.13$) among the three groups . We also observed no difference in the need for additional doses of analgesics between the three groups ($F_{2,62} = 1.18$, $P = 0.41$) despite the different dosages of intra-operative narcotics administered based on OSA severity. There was also no difference in emergence time between the groups ($F_{2,62} = 0.07$, $P = 0.93$). However, the recovery times were noticeably different between the groups ($F_{2,62} = 3.59$, $P < 0.05$) with group 3 (severe OSA) being significantly lower compared to the others (post-hoc multiple comparisons, Tukey HSD, $P < 0.05$). Results are shown graphically in Figure 3.

3.3. Regression analysis

We sought to determine the relationship between PSG indices and recovery times as a linear function. An equation that best models the linear relationship between the two variables as well as the goodness of fit was obtained.

AHI *vs* emergence and recovery time showed an overall negative relationship (Figure 4). This was statistically significant for the relationship between PACU recovery time and AHI ($F_{1,63} = 4.64$, $P < 0.05$). A similar analysis was carried out for SpO_2 nadir *vs* emergence and recovery time (Figure 4). The relationship was positive in this instance and was statistically significant for recovery time *vs* SpO_2 nadir ($F_{1,63} = 4.35$, $P < 0.05$).

4. Discussion

Obstructive sleep apnea in childhood is characterized by intermittent interruption of airflow during sleep which may be partial or complete, and is usually accompanied by episodes of snoring, desaturation, hypercapnia and arousals [1,19,20]. Left untreated, pediatric OSA disrupts physiological cycles of growth and development and has far-reaching consequences on behavior and cognition, cardiovascular function, autonomic regulation and inflammation [21–25].

Adenotonsillectomy has been recommended as the gold standard for treatment of childhood OSA [6,26]. Due to the large volumes performed annually (~500,000/year), this surgical procedure mandates a close understanding of altered respiratory physiology consequent to chronic intermittent hypoxemic states in OSA [27]. Previous work has highlighted quantitative changes in opioid receptors in the brainstem that leads to increased sensitivity to their depressant effects in these individuals[28]. This draws attention to peri-operative pharmacologic management of these patients to improve outcomes, reduce adverse events and surgical costs. The knowledge that a pediatric patient with OSA is more sensitive to the respiratory effects of opioids and benzodiazepines intuitively suggests that it could be beneficial to reduce opioid/premedication dosing with increasing severity of OSA without compromising on pain control. Raghavendran et al. retrospectively studied adverse events during adenotonsillectomies in historic cohorts that presented with OSA [29]. Equivalence in morphine dosing was compared between OSA and control subjects with desaturation events scored by the McGill oximetry system. Not surprisingly, the most

severe events were reduced significantly in the population with OSA by appropriately scaling down opioid dosing.

Children who are exposed to the effects of hypoxemia during development have altered physiologic responses to drugs with either opioid or benzodiazepine moieties [30]. These changes are most pronounced for cardiopulmonary reflex arcs originating or routed via the brainstem and may be principally mediated by μ-opioid receptors [31]. Evidence from animal models of intermittent hypoxia demonstrates an attenuated respiratory responses to hypoxia during development and shift in dominance from excitatory (glutamate-derived) to inhibitory (GABA-derived) responses that may render the respiratory system vulnerable to anesthetic stress [32]. Given these patterns of changes in brainstem respiratory nuclei, it is conceivable that opioids and benzodiazepines that activate μ-opioid and GABA receptors respectively could cause changes in respiratory control during surgical procedures. The increased incidence of respiratory complications may thus be closely correlated with patterns of activity triggered by alterations in endogenous neurotransmitters by protocols of analgesic and sedative drugs. In addition to opioids and benzodiazepines, muscle relaxants are also implicated in adverse respiratory events due to their residual effects which can persist for up to 2 hours after administration [33]. No muscle relaxants were used in our anesthesia protocol and the results suggest that even empiric reductions in doses of certain peri-operative medications could positively impact emergence and recovery from anesthesia after adenotonsillectomy for pediatric OSA.

The **routine admission** of very young children following surgery for OSA in a unit with overnight pulse oximetry with high nurse-to-patient ratios undoubtedly increases healthcare costs. The use of an alternate protocol that circumvents the negative effects of intraoperative opioids without compromising pain control has the potential to mitigate the need for prolonged observation. Thus far, despite relatively consistent evidence demonstrating the depressant effects of opioids, no controlled study has attempted to investigate titration of peri-operative opioids and/or benzodiazepines based on the severity of OSA in children. The incidence of respiratory depression seen with opioids extends well

beyond the time spent in the OR and does not necessarily correlate with the state of wakefulness [34]. The regression analysis in this study appears to suggest that recovery time and the incidence of adverse airway events may be effectively reduced by careful, severity-based titration of opioids and benzodiazepines. In our study, inversely titrating the above drugs to the severity of OSA resulted in earlier emergence and lower respiratory complications.

An important caveat concerning PACU discharge times merits further discussion. It is possible that despite meeting discharge criteria according to the protocol, the less severe OSA patients who were being sent home were observed for longer periods than the more severe ones who were admitted for overnight observation. Constraints of staffing and beds in the PACU could have prompted earlier transfer to the floor further confounding the observation. This may explain the paradoxical shortened recovery times seen in the severe OSA group which may be apparent rather than real. In addition, events on the floor were not systematically documented and some adverse events not requiring active intervention may have been missed.

This study was designed to observe factors that impacted recovery from anesthesia with attention to the severity of OSA and the impact of inverse titration of opioids. It has several inherent weaknesses; the most important being that the anesthetic protocol was not validated and the titration of opioids and benzodiazepines were based solely on the knowledge of increased sensitivity to those drugs in this condition. As stated previously, this was strictly an observational study where only the outcome variables were observed. In addition, the definitions used for mild, moderate and severe OSA are not the ones currently accepted for pediatric sleep apnea and some of the patients defined as moderate may have been severe and received a higher dose of hydromorphone. However, there are no validated and universally accepted indices to determine the severity of pediatric sleep apnea in children and most of the studies cited in the AAO-HNS guidelines to make their recommendations on that issue had an evidence quality of C [35]. Additionally, a candidate's thesis on PSG and **pediatric** OSA published by the Triological Society in 2007 used a similar non-evidence-based stratification of the severity of OSA [36].

Interestingly, what was observed was that tailoring the doses of drugs to the severity of OSA appeared to have a positive impact on recovery from anesthesia and may have circumvented some of the adverse events usually observed when conventional dosing is used. In the current study, we also could not separate the effects of the benzodiazepines and opioids, and thus cannot rule out their synergistic effects. It is also possible that the drug dosing alone was the single predictor in the study and the rest of the protocol did not affect outcomes. Future directions would include using a validated anesthesia protocol, randomizing groups to avoidance of midazolam completely; uniform reduced dosing of hydromorphone for all groups, and non-narcotic analgesic use in the PACU. However, execution of design and enrollment for such a study would be significantly harder due to parents' perception of randomization on issues of anxiety and pain control in a surgical setting [37]. Our overall goal in this study was to try and determine if reduced dosing with benzodiazepines and narcotic analgesics significantly impacted recovery outcomes without compromising on pain control and comfort. This we hope will result in making the procedure safer and more cost effective.

5. Conclusions

This study attempts to highlight the efficacy of tailored dosing of sedation and analgesia according to the severity of OSA in children undergoing adenotonsillectomy. It appears to be a reliable way of reducing the peri-operative period by improving emergence and recovery times. In addition, outcomes may be improved if adverse respiratory events are kept to the minimum and this along with the above will reduce the costs of the procedures. Our findings support the need to explore combinations of narcotic and non-narcotic agents administered at different times during the peri-operative period to positively impact outcomes for one of the most common surgical procedures performed in children.

6. Acknowledgements

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Figure Legends

Figure 1 Study design. Increased color intensity indicates dose titration based on severity of OSA. Both inhalational as well as IV formulations have been considered.

Figure 2 Demographic and polysomnographic characteristics of subjects enrolled in the study. (A-D) Histograms showing distribution of 4 key factors—(a) AHI (b) SpO_2 nadir (c) age and (d) **BMI z-score**. The mean ± s.d. of each distribution is plotted above their respective histogram.

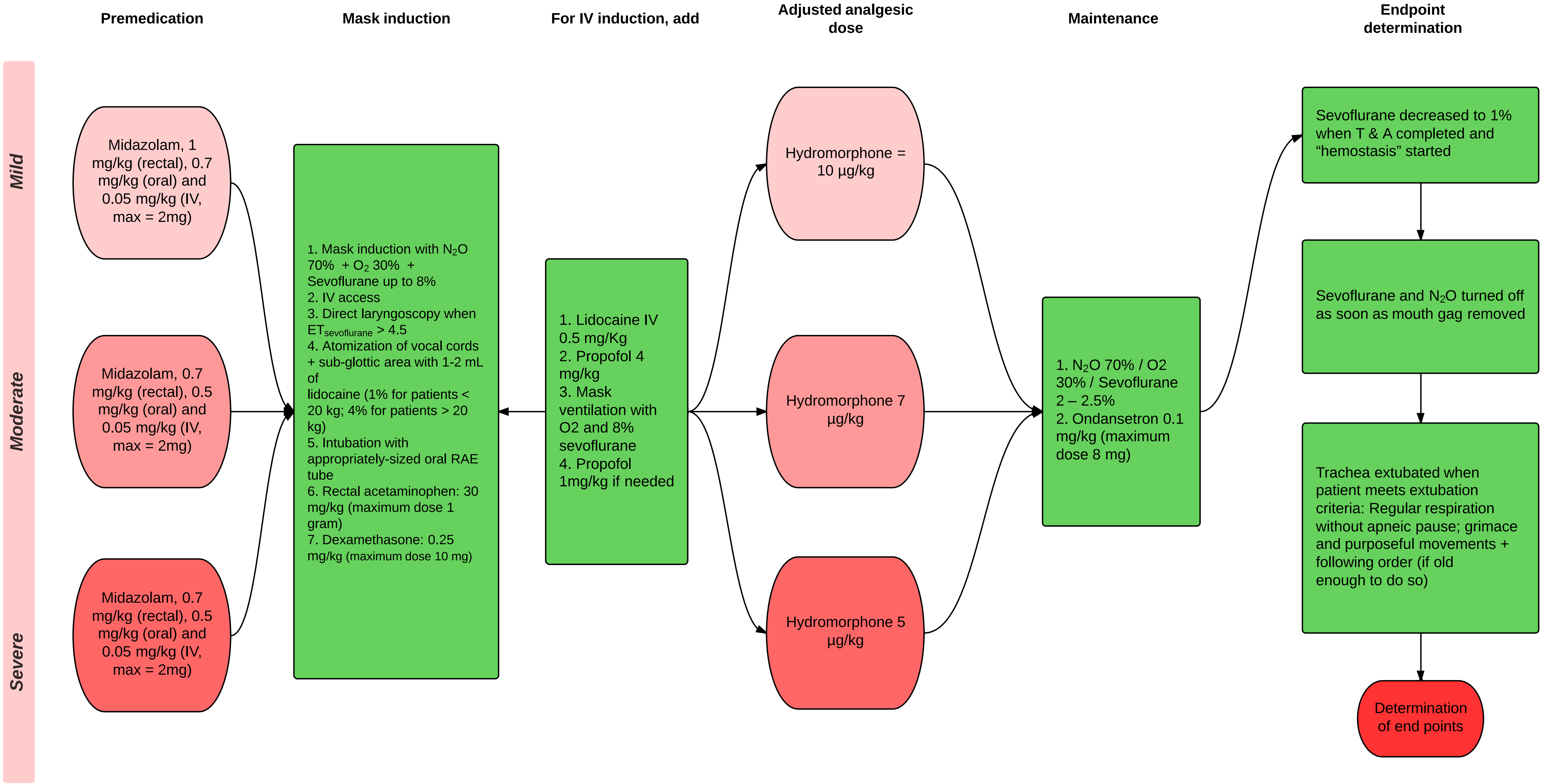
Figure 3 Cumulative distribution functions (cdfs) of chief PSG characteristics of enrolled subjects. (A-B) shows the distribution of emergence times (A) and discharge times (B). The barplots shown within the inset of each plot highlights overall differences between three groups stratified according to PSG-derived severity of OSA. Color legend signifying each group is shown between. *indicates $P < 0.05$.

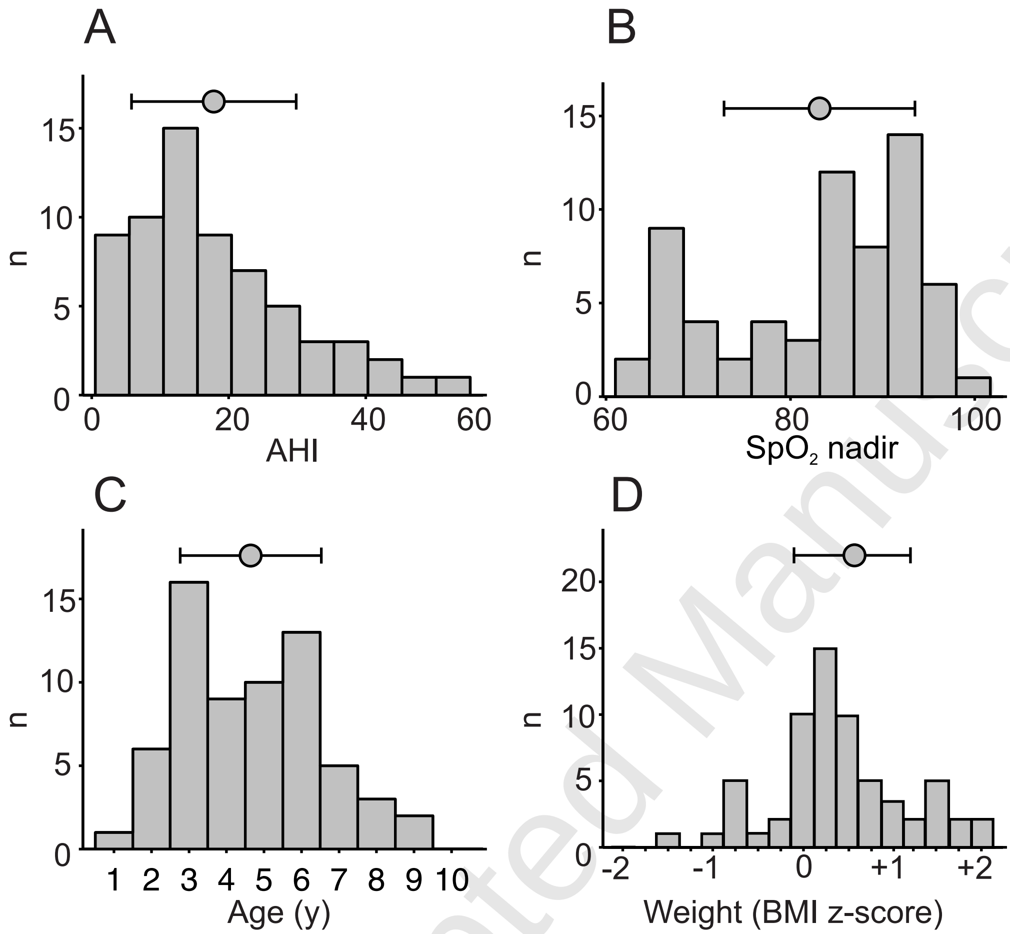
Figure 4 Relationship of PSG indices with recovery times. (A-B) and (C-D) represent results comparing emergence time with AHI (A) and SpO_2 nadir (B) respectively. Similarly, (C-D) shows results from a similar of distribution of discharge time as a function of AHI and SpO_2 respectively as above. Briefly, in (A,C), both metrics showed a significant inverse relationship with AHI. Similarly, (B-D) shows a positive relationship of SpO_2 nadir with recovery time. Results are shown in text.

Table 1 Inclusion and exclusion criteria for determining candidacy.

Inclusion criteria
• Patients aged 2-10 years
• Undergoing adenotonsillectomy
• Diagnosis of OSA, confirmed by polysomnography, and defined by AHI ≥ to 2
Exclusion criteria
• Patients aged > 10 years and < 2 years
• Obesity, as defined by normalized BMI ≥ 95^{th} percentile
• Craniofacial abnormalities or syndromes
• Contraindication to general anesthesia
• Additional procedures, with the exception of myringotomy and pressure equalization tubes or turbinate reduction.

Figure 1


Premedication
Mask induction
For IV induction, add
Adjusted analgesic dose
Maintenance
Endpoint determination
Mild
Moderate
Severe
Midazolam, 1 mg/kg (rectal), 0.7 mg/kg (oral) and 0.05 mg/kg (IV, max = 2mg)
Midazolam, 0.7 mg/kg (rectal), 0.5 mg/kg (oral) and 0.05 mg/kg (IV, max = 2mg)
Midazolam, 0.7 mg/kg (rectal), 0.5 mg/kg (oral) and 0.05 mg/kg (IV, max = 2mg)
1. Mask induction with N_2O 70% + O_2 30% + Sevoflurane up to 8%
2. IV access
3. Direct laryngoscopy when $ET_{sevoflurane}$ > 4.5
4. Atomization of vocal cords + sub-glottic area with 1-2 mL of lidocaine (1% for patients < 20 kg; 4% for patients > 20 kg)
5. Intubation with appropriately-sized oral RAE tube
6. Rectal acetaminophen: 30 mg/kg (maximum dose 1 gram)
7. Dexamethasone: 0.25 mg/kg (maximum dose 10 mg)
1. Lidocaine IV 0.5 mg/Kg
2. Propofol 4 mg/kg
3. Mask ventilation with O2 and 8% sevoflurane
4. Propofol 1mg/kg if needed
Hydromorphone = 10 µg/kg
Hydromorphone 7 µg/kg
Hydromorphone 5 µg/kg
1. N_2O 70% / O2 30% / Sevoflurane 2 – 2.5%
2. Ondansetron 0.1 mg/kg (maximum dose 8 mg)
Sevoflurane decreased to 1% when T & A completed and "hemostasis" started
Sevoflurane and N_2O turned off as soon as mouth gag removed
Trachea extubated when patient meets extubation criteria: Regular respiration without apneic pause; grimace and purposeful movements + following order (if old enough to do so)
Determination of end points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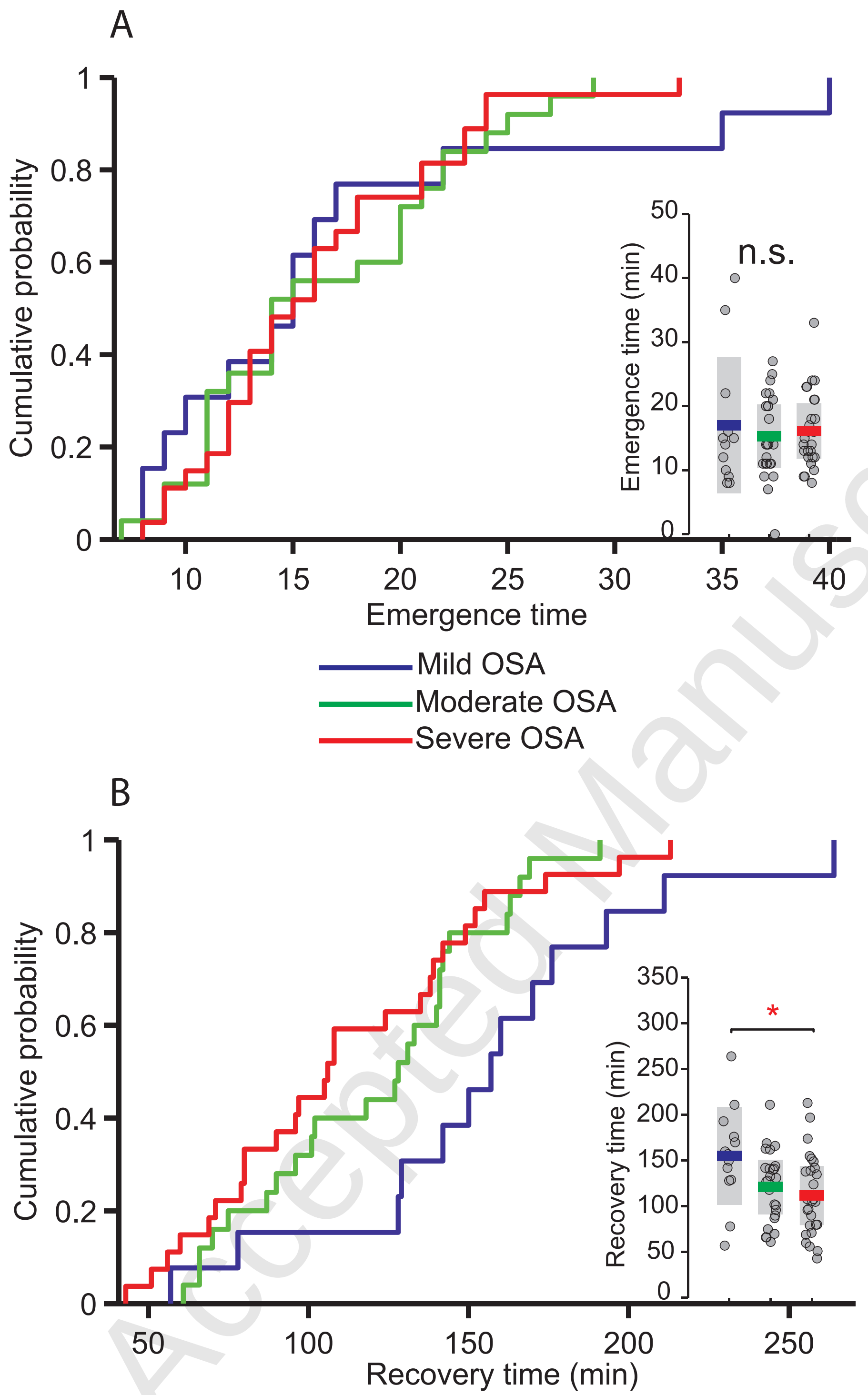
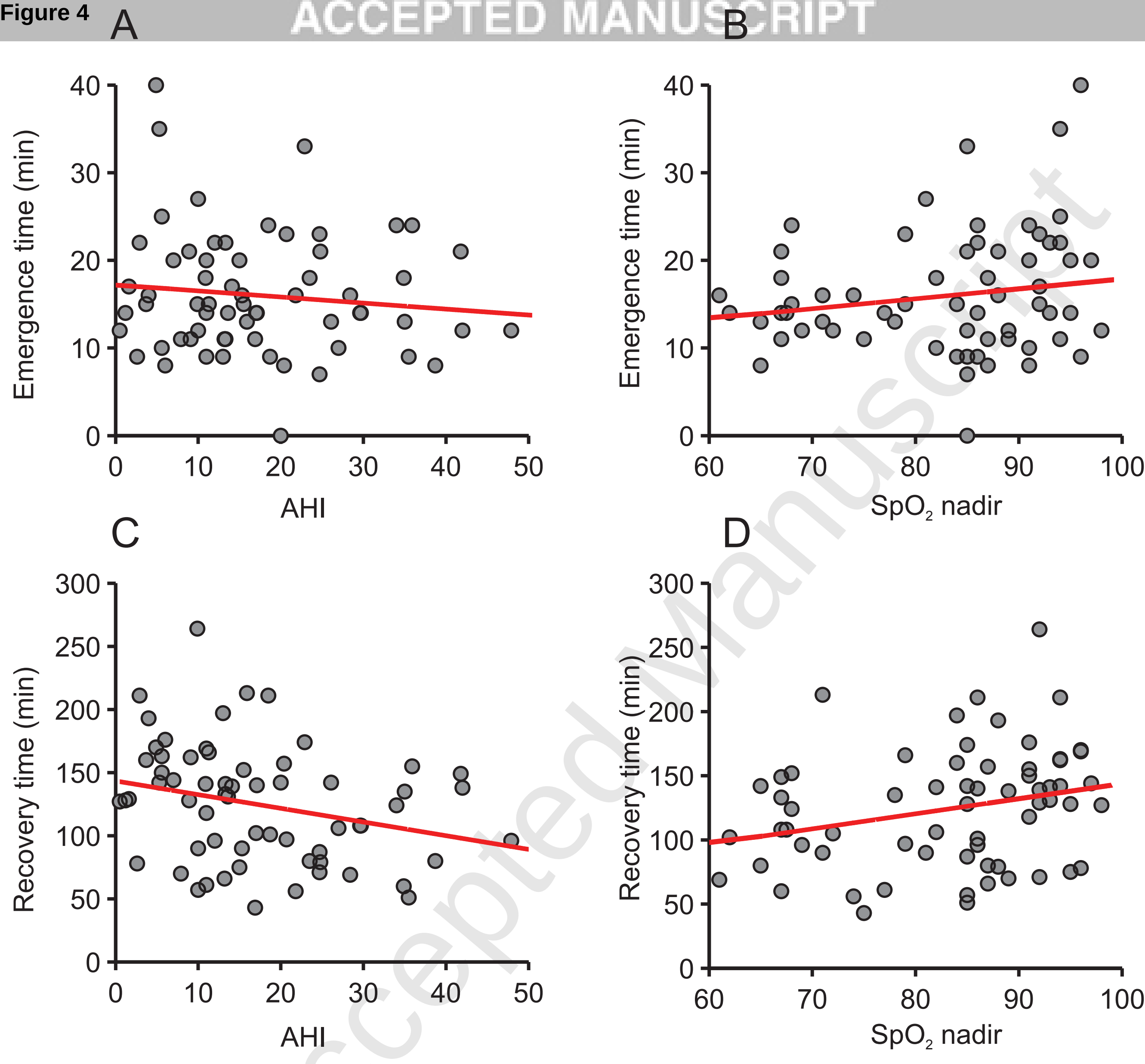
+1
+2
Weight (BMI z-score)



A
Cumulative probability
1
0.8
0.6
0.4
0.2
0
10
15
20
25
30
35
40
Emergence time
Emergence time (min)
50
40
30
20
10
0
n.s.
Mild OSA
Moderate OSA
Severe OSA
B
Cumulative probability
1
0.8
0.6
0.4
0.2
0
50
100
150
200
250
Recovery time (min)
Recovery time (min)
350
300
250
200
150
100
50
0
*

Figure 4


A
B
C
D
Emergence time (min)
Recovery time (min)
AHI
SpO₂ nadir
0
10
20
30
40
50
60
70
80
90
100
150
200
250
300